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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : ORLEK, Barry, Sidney [GB/GB]; BROWN, Thomas, Henry [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). COOPER, David, Gwyn [GB/GB]; Smithkline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).

(74) Agent: FLORENCE, Julia, A.; Corporate Patents, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

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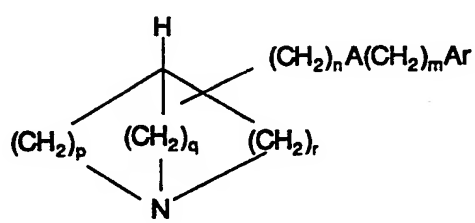

(I)

(57) Abstract

Use of compounds of formula (I), in which p, q and r each independently represent an integer from 1 to 4; A is a bond, -CH=CH-, -C≡C-, oxygen, sulphur or NR^1, where R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl; n is 0 to 6, and m is 0 to 6, such that the length of the chain $-(CH_2)_nA(CH_2)_m$ is at least two atoms; and Ar is aryl or heteroaryl, each of which may be optionally substituted; and pharmaceutically acceptable salts thereof, for the manufacture of a medicament for the treatment of disorders where a calcium channel antagonist is indicated. Novel compounds of formula (I), processes for preparing them and pharmaceutical compositions containing them are also described.

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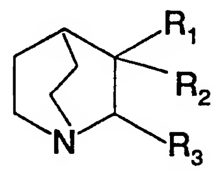
AZABRICYCLIC COMPOUNDS AS CALCIUM CHANNEL ANTAGONISTS

The present invention relates to the use of known and novel azabicyclic derivatives in therapy, in particular as calcium channel antagonists, novel compounds <u>per se</u>, processes for their preparation, and pharmaceutical compositions containing them.

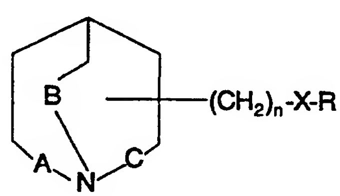
US Patent No. 4,599,344 describes quinuclidines of the formula :



wherein R_1 is <u>inter alia</u> hydrogen, R_2 is hydrogen or ALK-Z and R_3 is hydrogen or ALK"-Z, where ALK is C_{2-4}alkyl, ALK" is C_{1-4}alkyl and Z is a mono- or- di-substituted phenyl ring. These compounds are said to be antiarrhythmic agents.

Ricciardi and Doukas (Heterocycles, Vol 24, No 4, p971, 1986) describe certain styrylquinuclidines, which are said to inhibit cholineacetyl-transferase *in vitro*.

German OLS 41 16582 describes azabicyclic compounds of the formula :

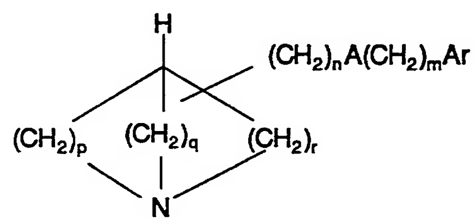


wherein A, B and C independently represent $-CH_2-$ or a single bond; n is zero, 1 or 2; X is oxygen or sulphur and R is <u>inter alia</u> phenylalkyl, diphenylalkyl, heterocyclicalkyl, phenyl, diphenyl or a heterocycle, each of which may be optionally substituted. These compounds are said to be useful as muscarinic antagonists.

EPA 497415 describes 3-(substituted phenoxy and substituted phenylthio)quinuclidines, wherein the phenyl substitutent is selected from <u>inter alia</u> lower alkoxy, lower aralkyloxy, halogen, NO_2, CF_3, CN and NR_1R_2, which compounds are said to be muscarinic agonists.

We have now found that certain substituted azabicyclic derivatives, including some of the above compounds, exhibit activity as calcium channel antagonists. They are thus of potential use in the treatment of disorders where calcium channel blockade is indicated, in particular disorders related to an accumulation of calcium in the brain cells of mammals.

The present invention therefore provides, in a first aspect, the use of a compound of formula (I):



Formula (I)

in which

p, q and r each independently represent an integer from 1 to 4;
A is a bond, -CH=CH-, -C≡C-, oxygen, sulphur or NR^1, where
R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl;

n is 0 to 6, and m is 0 to 6, such that the length of the chain $-(CH_2)_nA(CH_2)_m$ is at least two atoms; and

Ar is aryl or heteroaryl, each of which may be optionally substituted;

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of disorders where a calcium channel antagonist is indicated.

The H atom is shown on the bridgehead carbon atom to make clear that the $(CH_2)_nA(CH_2)_mAr$ chain cannot be attached at this position.

The compounds of formula (I) have been found to exhibit high calcium influx blocking activity for example in neurons. As such the compounds are expected to be of use in therapy, particularly in treating conditions and diseases related to (e.g. caused or exacerbated by) an accumulation of calcium in the brain cells of mammals, in particular humans. For example, the compounds are expected to be of use in the treatment of

anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction withdrawal such as ethanol addiction withdrawal.

In a further aspect of the invention there is also provided a method of treatment of conditions or diseases related to (e.g. caused or exacerbated by) the accumulation of calcium in the brain cells of mammals which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. Thus, for example, the present invention provides a method of treatment of anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction withdrawal such as ethanol addiction withdrawal, which comprises administering to a subject in need thereof, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In the compounds of formula (I) p and r are preferably independently 2 or 3; most preferably both are 2.

q is preferably 1 or 2.

The values of m and n should be chosen such that the length of the chain $(CH_2)_nA(CH_2)_m$ is at least 2 atoms. In general the length of the chain $-(CH_2)_nA(CH_2)_m$ is from 2 to 6 e.g. 2 to 5 atoms. Preferred values for n and m depend on the group A. Thus for example when A is oxygen the sum of n+m is preferably from 1 to 5, for example n may be 1, 2, 3 or 4 and m may be 0 or 1.

When A is a bond the sum of n+m should be at least 2, e.g. n+m may be 2 or 3. When A is CH=CH one or both of n and m may be zero, e.g. n may be zero or 1 and m may be zero.

A is preferably oxygen, a bond or -CH=CH-; most preferably A is oxygen.

When Ar represents aryl, suitable groups include, for example, unsaturated monocyclic and unsaturated or partially saturated bicyclic or tricyclic ring systems of up to 15 carbon atoms, such as, for example, phenyl, naphthyl, tetrahydronaphthyl, fluorene, fluorenone, dibenzosuberene and dibenzosuberenone. Preferred are optionally substituted phenyl rings.

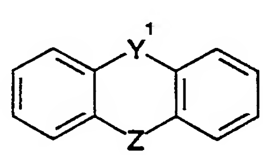
An aryl group may be substituted, for example, by a C_{1-2}alkylenedioxy group (e.g. phenyl substituted by a 3,4-methylenedioxy group) or by 1 to 3 substituents selected from halogen, C_{1-4}alkoxy, nitro, SC_{1-4}alkyl, $NR^{2a}R^{2b}$ (in which R^{2a} R^{2b} can be independently H or C_{1-4}alkyl), OCF_3, C_{1-6}alkyl, trifluoromethyl, CN, optionally substituted phenyl, optionally substituted phenoxy, optionally substituted phenylC_{1-4}alkyl and optionally substituted phenylC_{1-4}alkoxy.

Suitable optionally substituted phenylC_{1-4}alkyl groups include, for example benzyl. Suitable optionally substituted phenylC_{1-4}alkoxy groups include, for example benzyloxy groups.

Suitable substituents for said optionally substituted phenyl, phenoxy, phenylC_{1-4}alkyl and phenylC_{1-4}alkoxy groups include for example halogen, C_{1-4}alkyl, C_{1-4}alkoxy, nitro and trifluoromethyl groups.

Preferably the aryl group is a phenyl ring substituted by one or two substituents, in particular, by a phenyl; phenyl(C_{1-4})alkyl, e.g. benzyl or phenethyl; phenoxy; or phenylC_{1-4}alkoxy group; which groups may themselves be optionally substitued by halo, e.g. chloro.

When Ar represents heteroaryl suitable groups include, for example, unsaturated or partially saturated bicyclic and tricyclic ring systems containing at least one heteroatom. A bicyclic ring system preferably contains 8 to 10 ring members, such as quinolinyl, tetrahydroquinolinyl or benzofuranyl. A tricyclic ring system preferably contains from 11 to 15 ring members, and most preferably has the structure :



wherein Y^1 represents $Y(CH_2)_t$, Y is O, S or NR^3 (where R^3 is hydrogen or C_{1-4}alkyl), Z is $(CH_2)_s$ or -CH=CH-, s is 0, 1 or 2 and t is 0 or 1 or is a corresponding dehydro ring system. Examples of tricyclic heteroaryl groups include dibenzofuranyl, dibenzothienyl, carbazole, N-methylcarbazole, acridine and dibenzoxepine. The heteroaryl ring can be linked to the remainder of formula (I) via any suitable ring atom.

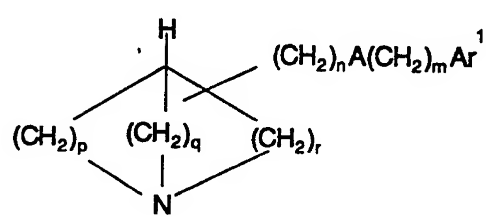
Suitable substituents for said heteroaryl rings

include, for example, 1 to 3 substituents selected from halogen, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, phenylC_{1-4}alkyl and phenylC_{1-4}alkoxy.

Alkyl groups present in the compounds of formula (I), alone or as part of another group, can be straight or branched. Thus a C_{1-4}alkyl group may be for example methyl, ethyl, n-propyl, n-butyl or any branched isomer thereof such as isopropyl or t-butyl.

It will be appreciated that for use in medicine a salt of a compound (I) should be pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, methanesulphonate or similar pharmaceutically acceptable inorganic or organic acid addition salts. Other non-pharmaceutically acceptable salts may be used for example in the isolation of a final product and are included within the scope of this invention.

The invention also provides novel compounds of formula (IA) :



Formula (IA)

in which

p, q and r each independently represent an integer from 1 to 4;
n is 0 to 6;
m is 0 to 6, and
either

A is -C≡C- or NR^1, where R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl; in which case Ar^1 represents the group Ar as hereinbefore defined;

or A is a bond, in which case Ar^1 represents the group Ar as hereinbefore defined with the proviso that when each of p, q and r is 2 and Ar is phenyl substituted by one or two groups selected from halogen, C_{1-4}alkoxy, nitro, cyano or amino, then the group $-(CH_2)_nA(CH_2)_m$ is not C_{1-4}alkyl α to the quinuclidine nitrogen atom or C_{2-4}alkyl β to the quinuclidine nitrogen atom,

or A is -CH=CH- in which case Ar^1 represents the group Ar as hereinbefore defined with the proviso that when each of p, q and r is 2; n and m are both zero and Ar is mono- or di-chlorophenyl, the group $-(CH_2)_nA(CH_2)_m$ is not β to the quinuclidine nitrogen atom.

or A is oxygen or sulphur in which case Ar^1 represents a group Ar^2 which is phenyl substituted by a C_{1-2}alkylenedioxy group or by 1 to 3 substituents selected from SC_{1-4}alkyl, OCF_3, CF_3, optionally substituted phenoxy, optionally substituted phenylC_{1-4}alkyl and optionally substituted phenylC_{1-4}alkoxy; or Ar^2 is

an optionally substituted bicyclic or tricyclic aryl group of up to 15 carbon atoms;

an optionally substituted benzofuranyl group; or an optionally substituted tricyclic heteroaryl group;

and salts thereof.

Suitable substituents for said optionally substituted phenoxy, phenylC_{1-4}alkyl and phenylC_{1-4}alkoxy groups are as hereinbefore defined.

Bicyclic and tricyclic aryl and heteroaryl groups for Ar^1 and Ar^2 include those defined hereinbefore for the group Ar.

In the compounds of formula (IA), p and r are preferably 2 or 3; q is preferably 1 or 2.

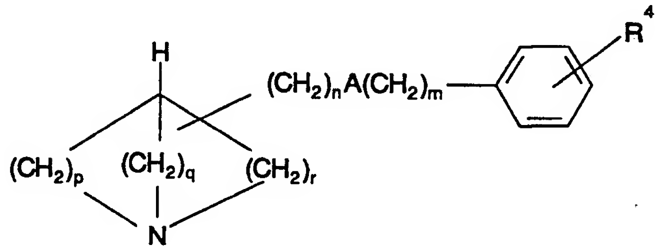
A is preferably O, -CH=CH- or a bond,
n is preferably zero, 1 or 2;
m is preferably zero or 1;
Ar^1 is preferably Ar^2 as defined above, or when A is -CH=CH or a bond Ar may also represent phenyl substituted by an optionally substituted phenyl group.

A bicyclic aryl group is preferably naphthyl.

A bicyclic heteroaryl group is preferably benzofuranyl.

A tricyclic heteroaryl group is preferably dibenzofuranyl.

A particular group of compounds according to the invention is that represented by formula (IB)

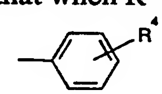


Formula (IB)

wherein p, q, r, n, m and A are as defined for formula (IA) and R^4 represents optionally substituted phenoxy, optionally substituted phenylC_{1-4}alkyl or optionally substituted phenylC_{1-4}alkoxy, or R^4 represents a fused benzene ring; and salts thereof.

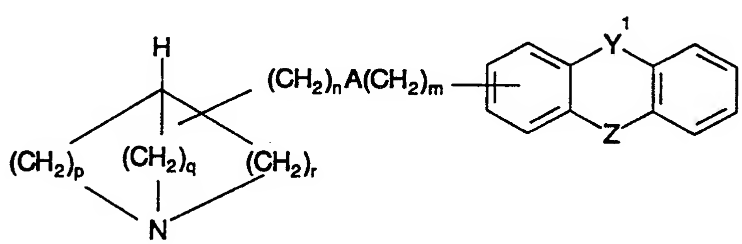
Preferred meanings for p, q, r, n, m, and A are as described for formula (IA).

Most preferably A represents oxygen.

It will be appreciated that when R^4 represents a fused benzene ring the group  is a naphthyl group.

R^4 preferably represents benzyl, benzyloxy or phenoxy, or is a fused benzene ring.

Another group of compounds according to the invention is that of formula (IC) :



Formula (IC)

wherein p, q, r, n, m and A are as defined for formula (IA) and Y^1 and Z are as hereinbefore defined for formula (I); and salts thereof.

Most preferably Y^1 is oxygen and Z is a bond.

Particular compounds of the invention include:

(±)3-(3,4-dichlorophenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-(4-benzyloxyphenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-(4-benzylphenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-(2-phenylphenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-(4-tert-butylphenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-(1-naphthyloxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-(2-dibenzofuranyloxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-(5-isoquinolinyloxy)methyl)-1-azabicyclo[2.2.2]octane hydrochloride,
(±) endo-3-(4-benzylphenoxymethyl)-1-azabicyclo[2.2.1]heptane hydrochloride,
(±) endo-3-(4-benzyloxyphenoxymethyl)-1-azabicyclo[2.2.1]heptane hydrochloride,
(±) exo-3-(4-benzylphenoxymethyl)-1-azabicyclo[2.2.1]heptane hydrochloride,
(±) exo-3-(4-benzyloxyphenoxymethyl)-1-azabicyclo[2.2.1]heptane hydrochloride,
(±) E-3-[2-(1-naphthyl)ethenyl]-1-azabicyclo[2.2.2]octane hydrochloride,
(±)E-3-[2-(4-biphenyl)ethenyl]-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-[2-(1-naphthyl)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-[2-(4-biphenyl)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride,
(±)E-3-[3-(1-naphthyl)prop-2-enyl]-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-[3-(1-naphthyl)propyl]-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-[2-(2-dibenzofuranyloxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-[2-(4-benzyloxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-[2-(4-benzylphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride,
(±)3-(4-phenoxyphenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride,

(±) 3-[2-(4-phenoxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride,

(±) 3-[4-(2-dibenzofuranyloxy)butyl]-1-azabicyclo[2.2.2]octane hydrochloride,

(±) 3-[4-(4-phenoxyphenoxy)butyl]-1-azabicyclo[2.2.2]octane hydrochloride,

(±) 3-[3-(4-phenoxyphenoxy)propyl]-1-azabicyclo[2.2.2]octane hydrochloride,

(±) 3-[2-[4-(2-phenylethyl)phenoxy]ethyl]-1-azabicyclo [2.2.2]octane hydrochloride,

(±) 3-[2-[4-[2-(4-chlorophenyl)ethyl]phenoxy]ethyl]-1-azabicyclo[2.2.2]octane hydrochloride,

(±) 3-[2-[5-(2-phenyl)benzo[b]furanyloxy]ethyl]-1-azabicyclo[2.2.2]octane hydrochloride,

(±) 2-[2-(4-benzylphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride,

(±) 2-[2-(4-benzyloxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride

(±) 2-[2-(4-phenoxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride, and

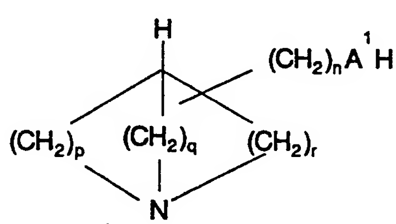
(±) 4-[2-(4-phenoxyphenoxy)ethyl]-1-azabicyclo[3.3.1]nonane hydrochloride.

It will be appreciated that the compounds of formula (I) may contain one or more asymmetric centres. Such compounds will exist as optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are included within the scope of the invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention. In addition, when A represents -CH=CH- the compounds will exist as geometric isomers, and the invention encompasses all such isomers and mixtures thereof.

In compounds of formula (I) having two asymmetric centres the stereochemical configuration in which the group $-(CH_2)_nA(CH_2)_mAr$ and the $(CH_2)_q$ bridge are on the same side of the plane of the molecule which contains both bridgehead atoms and the ring carbon bonded to the group $-(CH_2)_nA(CH_2)_mAr$ will herein be referred to as the **exo** configuration. Similarly the configuration of compounds in which the group $-(CH_2)_nA(CH_2)_mAr$ and the bridge $(CH_2)_q$ are on opposite sides of the above-mentioned plane will herein be referred to as the **endo** configuration. Both configurations are within the scope of this invention.

The compounds of the present invention can be prepared by processes analogous to those known in the art. The present invention therefore provides in a further aspect, a process for the preparation of a compound of formula (I) which comprises:

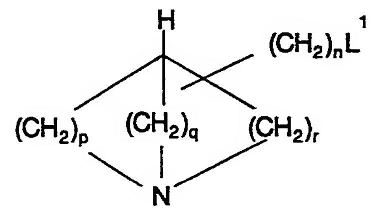
(a)for compounds of formula (I) in which A is O, S or NR^1, reaction of a compound of formula (II):



Formula (II)

in which p, q, r and n are as described for formula (I) and A^1 is O, S or NR^1, with a compound of formula $L(CH_2)_mAr$ in which m and Ar are as described for formula (I), and L is a leaving group;

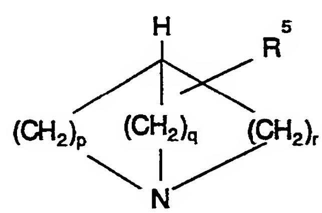
(b) for compounds of formula (I) in which A is O, S or NR^1, reaction of a compound of formula (III):



Formula (III)

in which p, q, r and n are as described for formula (I) and L^1 is a group displaceable by a nucleophile, with a compound of formula $HA^1(CH_2)_mAr$ where m and Ar are as described for formula (I) and A^1 is as described for formula (II); or

(c) for compounds of formula (I) in which A is NR^1, reduction of a compound of formula (IV) :



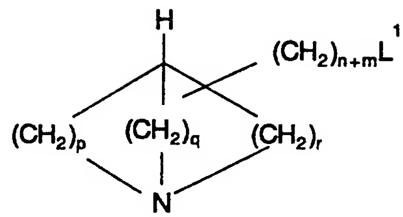
Formula (IV)

in which R^5 represents the group

$-(CH_2)_nN(R^1)C(O)(CH_2)_{m-1}Ar$ or $-(CH_2)_{n-1}C(O)N(R^1)(CH_2)_mAr$,

and p, q, r, n, m, and Ar are as described for formula (I);

(d) for compounds of formula (I) in which A is a bond, reaction of a compound of formula (V) :

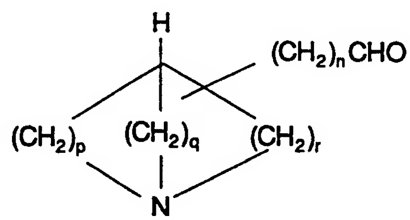


Formula (V)

(wherein L^1, p, q, r, m and n are as hereinbefore defined).

with a compound of formula X^1Ar in which Ar is as described for formula (I), and X^1 is an alkali metal;

(e) For compounds wherein A is -CH=CH- reaction of a compound of formula (VI) :



Formula (VI)

(wherein n, p, q and r are as hereinbefore defined) with a reagent serving to introduce the group Ar;

(f) Interconversion of one compound of formula (I) to a different compound of formula (I) e.g. the reduction of a compound wherein A is -CH=CH- to a compound wherein A is $-CH_2CH_2-$;

and optionally thereafter forming a salt.

In process (a) the reaction between a compound of formula (II) and a compound $L(CH_2)_mAr$ can take place under conditions which depend on the nature of the group L and the value of m. For example, when L is halogen or a sulphonic acid residue such as a tosylate or mesylate and m is other than zero, the reaction is carried out under standard conditions in a solvent, optionally in the presence of a base. When a fluoro-substituted aryl compound F-Ar is employed in process (a) (to prepare compounds where m is zero), the reaction is effected in the presence of a strong base such as sodium hydride, and in an

inert organic solvent such as dimethylformamide. Preferably the aryl group is substituted by an activating group such as CF_3 or NO_2. If necesary, the azabicyclic nitrogen atom may be protected during the reaction by methods well known in the art, e.g. by prior formation of a quaternary derivative such as an N-benzyl derivative. Protection may also be effected by formation of a borane (BH_3) complex. It will be appreciated that the N-protecting group should be chosen such that it can be removed without affecting other moieties in the molecule. Thus for example a benzyl protecting group may not be appropriate when the side chain $(CH_2)_nA(CH_2)_mAr$ also contains a benzyl moiety such as a benzyloxy group. In general, N-protection is preferred when the leaving group L represents halogen, e.g. bromine, but when L is a sulphonic acid residue e.g. a tosylate, N-protection may not be necessary.

The reaction between a compound of formula (III) and a compound of formula $HA^1(CH_2)_mAr$ (process (b)) can take place under conditions which depend on the nature of L^1 and A. For example when L^1 is hydroxy, m is 0 and A^1 is oxygen or sulphur the reaction is carried out in the presence of diethyl azodicarboxylate and triphenyl phosphine. Such a reaction is known as the Mitsunobu reaction (as described in Synthesis 1981, 1). Alternatively the leaving group L^1 may be for example a halogen atom or a sulphonyloxy group eg. methane-sulphonyloxy or p-toluene sulphonyloxy in which case the compound (III) may preferably be protected, e.g. as an acid salt, such as a hydrochloride salt. Reaction may be effected in the presence or absence of solvent, at a temperature in the range 0 to 200°C and may preferably be carried out in the presence of a base.

The reduction of a compound of formula (IV) according to process (d) can be effected by methods known in the art, for example using a reducing agent such as lithium aluminium hydride. Conveniently a compound of formula (IV) can be prepared (for example as described below) and reduced in a 'one-pot' reaction, without isolation of compound (IV) itself.

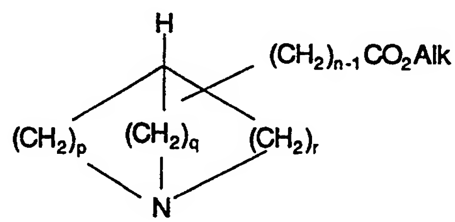
The reaction between a compound of formula (V) in process (d) and a compound of formula X^1Ar can take place under standard conditions known to those skilled in the art for the formation of carbon-carbon bonds.

Process (e) may be effected using a Wadsworth-Emmons reagent of the formula $Ar(CH_2)_{m+1}P(O)(OAlk)_2$, such as a diethylphosphonate, or a Wittig reagent of the formula $Ar(CH_2)_{m+1}PPh_3X$ (where X is an anion) which compounds are available commercially or can be prepared by known methods. The reaction may be carried out in a solvent such as tetrahydrofuran optionally containing a crown ether such as 15-crown-5, or

18-crown-6, and in the presence of a strong base such as sodium hydride or potassium t-butoxide.

Interconversion reactions according to process (f) may be effected by methods well known in the art. Thus for example conversion of a compound (I) wherein A represents -CH=CH- into a compound (I) wherein A represents-CH_2-CH_2- may be effected by catalytic reduction.

Compounds of formula (II) wherein n is 1 to 6 and A^1 is oxygen may be prepared by reduction of the corresponding ester of formula (VII) :



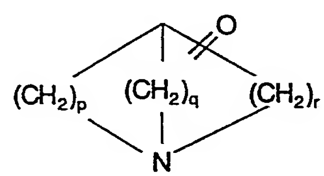
Formula (VII)

wherein p, q and r are as hereinbefore defined and Alk is a C_{1-6}alkyl group e.g. ethyl. The reduction may be effected using a reducing agent such as lithium aluminium hydride in a solvent such as diethyl ether or tetrahydrofuran. Esters of formula (VII) wherein n is 1 are described for example in European Patent Applications 257,741 and 392,803 and by B.S. Orlek et al, J. Med Chem, 1991, **34**, 2726 and Grob et al, Helv. Chim. Acta, 1957, **227**, 2170. Esters wherein n is greater than 1 may be prepared by conversion of an ester wherein n is 1 to the corresponding N-methyl-N-methoxycarboxamide (e.g. by hydrolysis of the ester followed by reaction with thionyl chloride and N, O-dimethylhydroxylamine hydrochloride), which is then reduced to the aldehyde using diisobutylaluminium hydride. The aldehyde is further converted to the cyanomethyl derivative for example as described in EPA 363,085, followed by acid hydrolysis, and esterification to form an ester wherein n is 2. The sequence may be repeated to form higher homologues.

Homologation may also be effected by the method described in British Patent No. 1250534, starting with a compound (II) wherein A^1 is O and n is 1 and proceeding via the corresponding halomethyl and cyanomethyl derivatives to an ester of formula (VII) wherein n is 2 which may be reduced to an alcohol (II) wherein n is 2.

A further method for the preparation of a compound of formula (II) wherein p, q, r and n each represent 2, A^1 is oxygen and the group $(CH_2)_nA^1H$ is α to the ring nitrogen atom involves cyclisation of a 4-piperidyl-but-2-enoic acid ester e.g. a methyl ester. The cyclisation is an intramolecular Michael reaction which may be carried out at elevated temperature in an inert solvent such as refluxing toluene. Methyl 4-piperidyl-but-2-enoate may be obtained from a suitable N-protected precursor such as methyl 4-(4-N-tert-butyloxycarbonylpiperidyl)-but-2-enoate (which may be prepared as described in EP 478363), using e.g. trifluoroacetic acid optionally in a solvent such as dichloromethane. Reduction e.g. with lithium aluminium hydride provides the above mentioned compound of formula (II).

Alternatively compounds of formula (II) may be prepared by reaction of an aldehyde of formula (VI) or a ketone of formula (VIII) :



Formula (VIII)

with triethylphosphonoacetate or triethylphosphonocrotonate, followed by catalytic hydrogenation to give an ethoxycarbonylalkyl derivative which is further reduced e.g. using lithium aluminium hydride, to the desired hydroxyalkyl compound. It will be appreciated that use of triethylphosphonoacetate results in a 2-carbon homologation whilst triethylphosphonocrotonate gives a 4-carbon homologation.

Compounds of formula (II) wherein n is zero may be prepared by reduction of a compound of formula (VII) e.g. using lithium aluminium hydride.

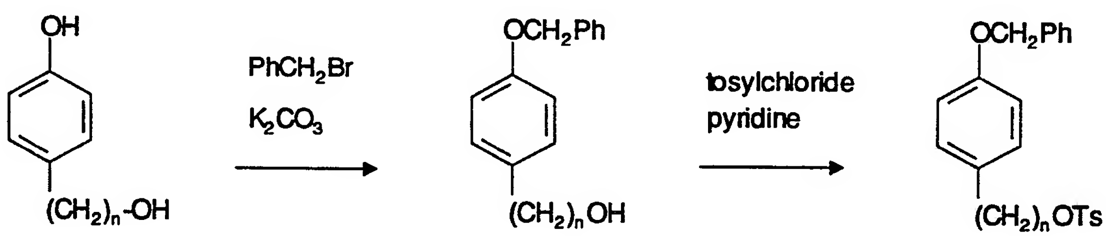
Ketones of formula (VIII) are commercially available or can be prepared by literature methods, generally via a Dieckmann cyclisation, (for example as described in EPA 94742).

Compounds of formula (II) wherein A^1 is S or NR^1 may be prepared from the corresponding hydroxy compound by standard methods, for example via formation of an alkyl halide followed by reaction with an appropriate amine or thiol.

Compounds of formula (III) wherein L^1 is OH can be prepared as described for compounds of formula (II), and compounds of formula (III) wherein L^1 is a halogen atom, or a mesyloxy or tosyloxy group can be prepared from the corresponding alcohol in conventional manner.

The compounds of formula $L(CH_2)_mAr$ and $HA^1(CH_2)_mAr$ may be prepared by standard methods well known in the art. For example compounds $L(CH_2)_mAr$ wherein Ar is a substituted phenyl group and L is halo, e.g. bromo, may be prepared by Friedel-Crafts acylation of the corresponding substituted benzene derivative, using an appropriate acid chloride and catalysed by aluminium trichloride, followed by reduction <u>in situ</u> with triethylsilane.

When Ar represents a phenyl group substitued by benzyloxy compounds $L(CH_2)_mAr$ may be prepared according to the following scheme :



The starting materials are available commercially or may be prepared by standard methods, e.g. by reaction of 4-benzyloxybenzaldehyde with triethylphosphonocrotonate in a similar manner to that described for the preparation of compounds (II).

Compounds of formula (IV) wherein R^5 is a group $-(CH_2)_nN(R^1)C(O)(CH_2)_{m-1}Ar$ can be prepared by reacting a compound of formula (II) wherein A^1 represents NR^1 with an acylating agent corresponding to the group $-(CH_2)_mAr$, for example an acid chloride $ClOC(CH_2)_{m-1}Ar$.

Compounds of formula (IV) wherein R^5 is a group $-(CH_2)_{n-1}C(O)N(R^1)(CH_2)_mAr$ may be prepared for example by reaction of a corresponding compound wherein R^5 represents $-(CH_2)_{n-1}CO_2H$ or an activated derivative thereof such as an acid halide, ester or anhydride, with an amine of formula $HN(R^1)(CH_2)_m$ Ar. It will be appreciated that when the acid itself is employed, reaction with the amine should be effected in the presence of a coupling agent. The carboxylic acid may itself be prepared for example by oxidation of the corresponding alcohol, ie. a compound of formula (II) wherein A^1 is oxygen.

Compounds of formula (V) may be prepared in analogous manner to compounds of formula (III); where necessary the chain length may be increased using methods well known in the art.

Compounds of formula (VI) may be prepared by conventional methods, for example the oxidation of a compound of formula (II) wherein A^1 is oxygen, or conversion of the corresponding ester, e.g. by hydrolysis and subsequent reaction with thionyl chloride and N,O-dimethyl-hydroxylamine, followed by reduction of the resulting N-methyl-N-methoxy-carboxamide, using diisobutylaluminium hydride. Compounds of formula (VI) wherein n is 1 may be prepared from the corresponding compound wherein n is zero by various methods. For example the aldehyde wherein n is zero may be treated with (methoxymethyl) triphenylphosphonium chloride and potassium t-butoxide, followed by a strong acid, e.g. concentrated sulphuric acid, resulting in the aldehyde wherein n is 1. Alternatively the aldehyde may be converted to the corresponding cyanomethyl derivative as described in EPA 363085 followed by acid hydrolysis, conversion to the N-methyl-N-methoxycarboxamide and reduction. These procedures may also be used to form higher homologues.

When a compound of formula (I) is obtained as a mixture of enantiomers, these may be separated by conventional methods such as crystallisation in the presence of a resolving agent, or chromatography, for example using a chiral HPLC column.

For use in medicine, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a novel compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

The compounds for use according to the invention may be administered by any convenient method for example by oral, parenteral, buccal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Compounds for use according to the invention may also be administered parenterally, by bolus injection or continuous infusion. Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Both liquid and solid compositions may contain other excipients known in the pharmaceutical art, such as cyclodextrins.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 60 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, eg. 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 60 mg, eg. 1 to 40 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Alternatively the compounds of the invention

may be administered by continuous intravenous infusion, preferably at a dose of up to 400 mg per day. Thus the total daily dosage by oral administration will be in the range 1 to 2000 mg and the total daily dosage by parenteral administration will be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL DATA

Ca^{2+} Current Measurement

Cell preparations

Sensory neurons from dorsal root ganglia were dissociated from 1 day old rat pups (Forda et al, Developmental Brain Research, 22 (1985), 55-65). Cells were plated out onto glass coverslips and used within 3 days to permit effective voltage clamp of Ca^{2+} currents.

Solutions

The pipette (internal solution) contained in mM: CsCl, 130; HEPES, 10; EGTA, 10; $MgCL^2$, 4; ATP, 2; buffered to pH 7.2 with CsOH. Cells were bathed in a normal Tyrodes solution before establishment of whole cell recording when the bathing solution was changed to one allowing isolation of Ca^{2+} currents. The external solution for recording Ca^{2+} channel currents contained in mM: $BaCL^2$, 10; TEA-Cl, 130; glucose, 10; HEPES, 10; $MgCL^2$, 1; buffered to pH 7.3 with TEA-OH. Barium was used as the charge carrier as this assists in current isolation and calcium dependent inactivation of current is avoided. Compounds were dissolved in DMSO to make a 20 mM stock solution. At the drug concentration used the vehicle (0.1%) had no significant effect on Ca^{2+} currents. All experiments were performed at 21 to 24°C. Whole cell currents were recorded using List EPC-7 amplifiers and stored, digitised for later analysis using PC based software similar to that described previously (Benham & Tsien, Journal of Physiology (1988), **404**, 767-784).

Ca^{2+} currents

Peak voltage gated Ca^{2+} channel currents of up to 10 nA from dorsal root ganglion neurons were recorded using 10 mM Ba^{2+} as charge carrier. Currents were evoked from a holding potential of -80 mV to a test potential of 0 or +10 mV every 15 seconds. This test potential was at the peak of the current voltage relationship and assessing block at this point reduced any errors due to drifting holding potential. Some cells showed slow rundown of current as is commonly seen when recording Ca^{2+} currents. The rundown rate was measured in control conditions and extrapolated through the time of drug

application to derive a control value to relate the drug affected current to. Block by 20 mM drug was assessed 3 minutes after drug application.

Compounds of the invention gave percentage inhibition of plateau Ca^{2+} current in the range 28 - 99%.

PHARMACEUTICAL FORMULATIONS

1. Formulation for intravenous infusion

Compound of formula (I)	0.1 - 60 mg
Sodium hydroxide/hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 30 ml
propylene glycol	0 - 30 ml
alcohol	0 - 10 ml
water	to 100 ml

2. Formulation for bolus injection

Compound of formula (I)	0.1 - 60 mg
sodium hydroxide or hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 2.5 ml
alcohol	0 - 2.5 ml
water	to 5 ml

A tonicity adjusting agent eg. sodium chloride, dextrose or mannitol may also be added.

3. Tablet for oral administration

	mg/tablet
Compound of formula (I)	25
lactose	153
starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	2
	255

The following non-limiting examples illustrate the preparation of compounds of formula (I) :

Preparation 1
(±)3-Hydroxymethyl-1-azabicyclo[2.2.2]octane

A solution of (±) methyl 1-azabicyclo[2.2.2]oct-3-yl-carboxylate (B.S. Orlek et al., J. Med. Chem., 1991, 34, 2726) (11g, 65mmol) in dry diethyl ether (100ml) was added over 0.5h to a stirred, ice cold suspension of lithium aluminium hydride (4.94g, 130mmol) in dry diethyl ether (200ml), under nitrogen. The reaction was allowed to warm to room temperature over 20 min and then quenched with wet ether followed by the minimum amount of water. The reaction was filtered and the precipitate was washed with 20% methanol in diethyl ether. The combined filtrate and washings were concentrated *in vacuo* and the resulting clear oil was distilled to afford the **title compound** as a colourless oil (7.55g) b.p. 150°C, 0.4mmHg (Kugelröhr) which solified on standing.

^{1}H Nmr ($CDCl_3$) δ : 1.33-1.93 (6H, m), 2.27-2.52 (2H, m), 2.68-2.89 (4H, m), 2.94-3.07 (1H, m), 3.57 (2H, d, J=8Hz)

Preparation 2
(±) endo-3-hydroxymethyl-1-azabicyclo[2.2.1]heptane

The title compound was prepared in a similar manner to Preparation 1 from (±) endo ethyl 1-azabicyclo[2.2.1]hept-3-ylcarboxylate (EP392803, Description 21) (2g, 11.8mmol) and lithium aluminium hydride (0.90g, 23.7mmol). This afforded the **title compound** as a white solid (1.22g) b.p. 150°C, 0.5mmHg (Kugelöhr).

^{1}H Nmr ($CDCl_3$) δ : 1.38-1.63 (2H, m) 1.83-2.00 (1H, m), 2.11-2.67 (5H, m), 2.75-3.03 (2H, m), 3.20-3.69 (3H, m).

Preparation 3
(±) exo-3-and endo-3-hydroxymethyl-1-azabicyclo[2.2.1]heptane

The title compound was prepared in a similar manner to Preparation 1 from (±) exo- and endo-ethyl 1-azabicyclo[2.2.1]hept-3-ylcarboxylate (EP392803, Description 22) (2g, 11.8mmol) and lithium aluminium hydride (0.90g, 23.7mmol). This afforded **title compound** as a clear oil (1.01g) b.p. 150°C, 0.5mmHg (Kugelröhr) consisting of a 6:1 mixture of exo and endo isomers.

^{1}H Nmr ($CDCl_3$) (Signals corresponding to the major exo- isomer) δ : 1.11-1.25 (1H, m), 1.53-1.71 (2H, m), 2.17-2.91 (7H, m) 3.28-3.51 (3H, m).

Preparation 4
(±)3-Formylmethyl-1-azabicyclo[2.2.2]octane

A suspension of potassium tert-butoxide (1.62g, 14.39mmol) in dry tetrahydrofuran (50ml), at -20°C, under nitrogen, was treated with (methoxymethyl)triphenylphosphonium chloride (4.93g, 14.39mmol) over 30 min. After stirring at -20°C for 30 min the reaction was treated with a solution of (±)1-azabicyclo[2.2.2]oct-3-ylcarboxaldehyde (EP363085, Description 32) (1g, 7.19mmol) in tetrahydrofuran (5ml). The reaction was stirred at -20°C for 1h, then quenched by the addition of 5N sulphuric acid (15ml). The separated aqueous layer was washed with chloroform (2x10ml), then cooled in ice and treated dropwise with concentrated sulphuric acid (3ml). After stirring for 1.5h at 0°C, the solution was basified with potassium carbonate, then extracted into chloroform (3x40ml). The combined organic extracts were dried over sodium sulphate then concentrated *in vacuo*. The residue was taken up in diethyl ether, filtered, then concentrated *in vacuo* and distilled to afford the **title compound** as a clear oil (0.42g) b.p. 175°C, 0.8mmHg (Kugelröhr).

Preparation 5
(±)3-(2-Hydroxyethyl)-1-azabicyclo[2.2.2]octane

The title compound was prepared in a similar manner to Preparation 1 from (±) 3-ethoxycarbonylmethyl-1-azabicyclo-[2.2.2]octane (EP 363085, Description 3), (8.72g, 44.3mmol) and lithium aluminium hydride (5.04g, 132mmol). This afforded the **title compound** as a clear oil (4.22g) b.p. 175°C, 0.2mmHg (Kugelröhr).

^{1}H Nmr ($CDCl_3$) δ : 1.29-1.72 (8H, m), 2.30-2.41 (1H, m), 2.68-2.93 (5H, m), 3.00-3.13 (1H m), 3.55-3.66 (2H, t, J=7Hz).

Preparation 6
(±) 3-(3-Ethoxycarbonylpropyl)-1-azabicyclo[2.2.2]octane

A solution of 3-quinuclidinone (1.0g, 8.0 mmol) and triethyl 4-phosphonocrotonate (2.50g, 10.0 mmol) in dry tetrahydrofuran (10 ml) was added over 15 min to a stirred ice cold suspension of sodium hydride (0.30g of an 80% dispersion in mineral oil, 10.0 mmol)

in dry tetrahydrofuran (20 ml) containing 15-crown-5 (60 mg) under nitrogen. The reaction was allowed to warm up to room temperature. After 1.5 h further quantities of triethyl 4-phosphonocrotonate (0.625g, 2.5 mmol) and sodium hydride (0.075g of an 80% dispersion in mineral oil, 2.5 mmol) were added, and the mixture was left stirring overnight. The reaction was quenched with glacial acetic acid (1ml) and concentrated *in vacuo*. The residue was partitioned between aqueous saturated potassium carbonate (30 ml) and chloroform (30 ml). The aqueous phase was further extracted with chloroform (2x30 ml), and the combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. Treatment with ethereal hydrogen chloride afforded the hydrochloride salt (2.1g) which was dissolved in ethanol (40 ml) and hydrogenated over 10% Pd-C (0.5g) at atmospheric pressure for 1h. After removal of the catalyst by filtration through kieselguhr the filtrate was concentrated *in vacuo*. The residue was partitioned between saturated aqueous potassium carbonate (25 ml) and chloroform (25 ml). The aqueous layer was extracted with chloroform (2x25ml) and the combined organic extracts were dried over sodium sulphate and concentrated *in vacuo* to give the **title compound** as an oil (1.95g) which was used in the next stage without purification.

^{1}H Nmr ($CDCl_3$) δ : 1.20-1.75 (13H, m), 2.30 (3H, m), 2.80 (4H, m), 3.08 (1H, m), 4.12 (2H, q, J=6Hz)

Preparation 7

(±) 3-(4-Hydroxybutyl)-1-azabicyclo[2.2.2]octane

The title compound was prepared in a similar manner to Preparation 1 from (±) 3-(3-ethoxycarbonylpropyl)-1-azabicyclo[2.2.2]octane (1.94g) and lithium aluminium hydride (1.21g, 32 mmol). This afforded the **title compound** as an oil (1.0g, 68% based on 3-quinuclidinone) which solidified on standing and was used in the next stage without purification.

^{1}H Nmr ($CDCl_3$)δ: 1.22 - 1.78 (13H, m), 2.32 (1H, m), 2.77 (4H, m), 3.07 (1H, m), 3.62 (2H, t, J=6Hz)

Preparation 8

(±) 3-(2-Ethoxycarbonylethyl)-1-azabicyclo[2.2.2]octane

The title compound was prepared in a similar manner to Preparation 6 from (±) 1-azabicyclo[2.2.2]octan-3-yl carboxaldehyde (EP 363085, Description 32) (1.50g, 10.8 mmol), triethyl phosphonoacetate (2.78 ml, 14.0 mmol), sodium hydride (0.39g of an 80%

dispersion in mineral oil, 13.0 mmol) and 15-crown-5 (0.1g). After 1h at room temperature, the reaction was quenched with glacial acetic acid (1.5ml) and worked up as described in Preparation 6. Hydrogenation in ethanol (40 ml) over 10% Pd-C (0.5g) at atmospheric pressure afforded the **title compound** as an oil (1.97g, 86%) which was used in the next stage without purification.

^{1}H Nmr ($CDCl_3$) δ: 1.28 (3H, t, J=6Hz), 1.30-1.80 (8H, m), 2.20-2.40 (4H, m), 2.80 (4H, m), 3.10 (2H, m), 4.12 (2H, q, J=6Hz).

Preparation 9
(±) 3-(3-Hydroxypropyl)-1-azabicyclo[2.2.2]octane hydrochloride

The title compound was prepared in a similar manner to Preparation 1 from (±) 3-(2-ethoxycarbonylethyl)-1-azabicyclo[2.2.2]octane (1.97g, 9.34 mmol) and lithium aluminium hydride (1.06g, 27.9 mmol). Purification by flash chromatography on neutral alumina using 0-10% methanol in chloroform as eluant, followed by distillation afforded the **title compound** as an oil (0.46g, 30%) b.p. 180°C, 0.2 mmHg (Kugelrohr).

^{1}H Nmr ($CDCl_3$)δ: 1.28-1.78 (10H, m), 2.35(1H, m), 2.75 (4H, m), 2.90-3.12 (1H, m and 1H, br s), 3.60 (2H, t, J=6Hz).

Preparation 10
(±) 2-(2-Methoxycarbonylmethyl)-1-azabicyclo[2.2.2]octane

A solution of methyl 4-(4-N-t-butyloxycarbonylpiperidinyl)-but-2-enoate (EP 478363) (5.0g, 17.67 mmol) in dry dichloromethane (50ml) was treated with trifluoroacetic acid (10ml) and the mixture was stirred at room temperature for 24h. The reaction was concentrated *in vacuo*, cooled in ice and treated with a saturated aqueous solution of potassium carbonate (75ml). After exhaustive extraction with chloroform the combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. The residue was extracted into diethyl ether, and insoluble impurities removed by filtration. The filtrate was concentrated *in vacuo*. The residue was dissolved in dry toluene (200ml) and heated under reflux in a nitrogen atmosphere for 12h. The reaction was concentrated *in vacuo* and the residue was distilled to give the title compound as a colourless oil (2.8g, 88%) b.p. 135°C at
0.2 mm Hg (Kugelrohr).

^1H Nmr ($CDCl_3$) δ: 1.10 (1H, m); 1.50 (4H, m); 1.80 (2H, m); 2.45 (1H, dd, J=15Hz and 7Hz); 2.60 (1H, dd, J= 15Hz and 7Hz); 2.73 (1H, m), 2.95 (3H, m); 3.30 (1H, m); 3.68 (3H, s).

Preparation 11
(±) 2-(2-Hydroxyethyl)-1-azabicyclo[2.2.2]octane

The title compound was prepared in a similar manner to Preparation 1 from (±) 2-(2-methoxycarbonyl-methyl)-1-azabicyclo [2.2.2] octane (2.1g, 11.48mmol) and lithium aluminium hydride (1.74g, 45.90mmol) employing a reaction time of 2h at room temperature. This afforded the title compound as a colourless solid (1.67g, 94%) b.p. 180°C at 0.1 mm Hg (Kugelrohr).

Preparation 12
4-[2-(4-Chlorophenyl)ethyl]phenol

A solution of 4-chloro-4'-hydroxystilbene (5.43g) in ethanol (80ml) was hydrogenated over 5% Pd-C (1.0g) at atmospheric pressure for 1h. Catalyst was removed by filtration through kieselguhr. The filtrate was concentrated *in vacuo* and distilled to give the **title compound** as a colourless solid (4.66g, 85%) b.p. 250°C, 0.1 mm Hg (Kugelrohr)

Preparation 13
2-Phenyl-5-hydroxybenzo[b]furan

A solution of 2-phenyl-5-methoxybenzo[b]furan (K K Thomas and M M Bokadia, J Indian Chem. Soc. 1966, 43, 713) (0.5g, 2.23 mmol) in absolute chloroform (4 ml) was treated with trimethylsilyl iodide (0.44 ml, 3.09 mmol) and warmed at 50°C for 48h. A further quantity (0.22ml) of trimethylsilyl iodide was added during this period. The reaction mixture was diluted with methanol (20 ml), treated with brine (40 ml) and extracted into diethyl ether (2x40ml). The combined extracts were washed with aqueous sodium metabisulphite, followed by brine (40ml) and dried over sodium sulphate. After concentration *in vacuo* the residue was distilled to give the **title compound** as a colourless solid (0.41g, 88%) b.p. 250°C, 0.1 mm Hg (Kugelrohr).

Preparation 14
(±) 4-Ethoxycarbonylmethyl-1-azabicyclo[3.3.1]nonane

To a solution of triethyl phosphonoacetate (2.62ml, 13.19mmol) in dry N, N-dimethylformamide (13ml) cooled to 0°C under nitrogen was added potassium t-butoxide (1.16g, 10.36mmol) portionwise over 30 min. After stirring at 0°C for 45 min the mixture was cooled to -10°C and treated dropwise with a solution of 1-azabicyclo [3.3.1]nonan-4-one (1.3g, 9.42 mmol) in dry N, N-dimethylformamide (7ml). The reaction was allowed to warm to room temperature and after 6 h quenched below 0°C with excess glacial acetic acid. The mixture was concentrated *in vacuo* and the residue was treated with 2M orthophosphoric acid (30ml), and washed exhaustively with diethyl ether. The aqueous layer was saturated with potassium carbonate and extracted into chloroform (3x30ml). The combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography on neutral aluminia using 0-2% methanol in chloroform as eluant. The major faster running component was hydrogenated in ethanol (25 ml) over 5% Pd-C (0.2g) at atmospheric pressure for 4h. The catalyst was removed by filtration through kieselguhr, and the filtrate was concentrated *in vacuo*. The residue was partitioned between aqueous saturated potassium carbonate (15ml) and chloroform (15ml). The aqueous phase was extracted with chloroform (2x15ml) and the combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. Chromatography on silica using 2-15% methanol in chloroform as eluant afforded the **title compound** as a clear oil (0.19g).

Preparation 15
(±) 4-(2-Hydroxyethyl)-1-azabicyclo[3.3.1]nonane

The title compound was prepared in a similar manner to Prepartion 1 from (±) 4-ethoxycarbonylmethyl-1-azabicyclo [3.3.1] nonane (0.18g, 0.86mmol) and lithium aluminium hydride (65mg, 1.71mmol). This afforded the **title compound** as a clear oil (0.12g, 83%) b.p. 190°C, 0.2mmHg (Kugelrohr).

Example 1

(±)3-(3,4-Dichlorophenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride (E1)

A solution of (±) 3-hydroxymethyl-1-azabicyclo[2.2.2]octane (0.5g, 3.55mmol) in dry tetrahydrofuran (40 ml), under nitrogen, was treated with 3,4-dichlorophenol (0.867g, 5.32mmol) in dry tetrahydrofuran (2 ml), then treated with triphenylphosphine (1.21g, 4.61mmol) in tetrahydrofuran (2 ml). Diethyl azodicarboxylate (0.80g, 4.61mmol) was added to the reaction over 0.5 h and the mixture was stirred overnight at room temperature. The reaction was concentrated *in vacuo* treated with saturated aqueous potassium carbonate (25ml), then extracted into chloroform (3x25ml). The combined organic extracts were dried over sodium sulphate, concentrated *in vacuo* and the residue chromatographed on neutral alumina in a gradient of 0-2% methanol in chloroform. The gum produced was converted to the HCl salt, which was washed thoroughly with diethyl ether then crystallised to afford the **title compound** as a white solid (0.78g) m.p. 194-197°C (from methanol - diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.61-2.12 (5H, m), 2.38-2.54 (1H, m), 2.83-2.94 (1H, m), 3.04-3.45 (5H, m), 4.10 (2H, d, J=Hz), 6.98 (1H, dd, J=4, 9Hz), 7.28 (1H, d, J=4Hz), 7.53 (1H, d, J=9Hz).

Example 2

(±)3-(4-Benzyloxyphenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride (E2)

The title compound was prepared in a similar manner to Example 1 from (±)3-hydroxymethyl-1-azabicyclo[2.2.2]octane (2g, 14.2mmol), 4-(benzyloxy)phenol (8.52g, 42.6mmol), triphenylphosphine (4.84g, 18.4mmol) and diethyl azodicarboxylate (3.21g, 18.4mmol). This afforded the **title compound** as a white solid (3g) m.p. 205-207°C (from methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.64-2.13 (5H, m), 2.38-2.52 (1H, m), 2.83-2.91 (1H, m), 3.07-3.46 (5H, m), 3.98 (2H, d, J=8Hz), 5.05 (2H, s), 6.86-6.99 (4H, m), 7.28-7.46 (5H, m)

Example 3

(±)3-(4-Benzylphenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride (E3)

The title compound was prepared in a similar manner to Example 1 from (±)3-hydroxymethyl-1-azabicyclo[2.2.2]octane (0.5g, 3.55mmol), , 4-hydroxydiphenylmethane (0.98g, 5.32mmol), triphenylphosphine (1.21g, 4.61mmol) and diethyl azodicarboxylate (0.80g, 4.61mmol). This afforded the **title compound** as a white solid (0.46g) m.p. 169-171°C (methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.60-2.12 (5H, m), 2.36-2.51 (1H, m), 2.80-2.92 (1H, m), 3.08-3.45 (5H, m), 3.85 (2H, s), 3.99 (2H, d, J=7Hz), 6.79-6.92 (2H, m), 7.07-7.31 (7H, m)

Example 4

(±)3-(2-Phenylphenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride (E4)

The **title compound** (E4) was prepared in a similar manner to Example 1 from (±)3-hydroxymethyl-1-azabicyclo[2.2.2]octane (0.5g, 3.55mmol), 2-phenylphenol (0.905g, 5.32mmol), triphenylphosphine (1.21g, 4.61mmol) and diethyl azodicarboxylate (0.80g, 4.61mmol). This afforded the **title compound** as a white solid (0.49g) m.p. 184-187°C (from methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.64-2.11 (5H, m), 2.42-2.57 (1H, m), 2.95-3.54 (6H, m), 4.16 (2H, d, 7Hz), 7.09-7.62 (9H, m).

Example 5

(±)3-(4-tert-Butylphenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride (E5)

The title compound was prepared in a similar manner to Example 1 from (±)3-hydroxymethyl-1-azabicyclo[2.2.2]octane (0.5g, 3.55mmol), 4-tert-butylphenol (0.80g, 5.32mmol), triphenylphosphine (1.21g, 4.61mmol) and diethyl azodicarboxylate (0.80g, 4.61mmol). This afforded the **title compound** (E5) as a white solid (0.35g) m.p. 276-279°C (from methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.24 (9H, s), 1.63-2.15 (5H, m), 2.39-2.53 (1H, m), 2.83-2.94 (1H, m), 3.08-3.47 (5H, m), 4.02 (2H, d, J=7Hz), 6.88 (2H, d, J=8Hz), 7.30 (2H, d, J=8Hz)

Example 6

(±)3-(1-Naphthyloxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride (E6)

The title compound was prepared in a similar manner to Example 1 from (±)3-hydroxymethyl-1-azabicyclo[2.2.2]octane (0.5g, 3.55mmol), 1-naphthol (0.77g, 5.32mmol), triphenylphosphine (1.21g, 4.61mmol) and diethyl azodicarboxylate (0.80g, 4.61mmol). This afforded the **title compound** as a white solid (0.18g) m.p. 206-208°C (from methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.60-1.72 (1H, m), 1.77-2.01 (3H, m), 2.11-2.20 (1H, m), 2.53-2.66 (1H, m), 2.89-3.01, (1H, m), 3.05-3.32 (4H, m), 3.41-3.53 (1H, m), 4.18 (2H, d, J=7Hz), 6.95 (1H, d, J=7Hz), 7.29-7.52 (4H, m), 7.75-7.84 (1H, m), 8.02-8.10 (1H, m).

Example 7

(±)3-(2-Dibenzofuranyloxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride (E7)

The title compound was prepared in a similar manner to Example 1 from (±)3-hydroxymethyl-1-azabicyclo[2.2.2]octane (0.5g, 3.55mmol), 2-hydroxy-dibenzofuran (0.98g, 5.32mmol), triphenylphosphine (1.21g, 4.61mmol) and diethyl azodicarboxylate (0.81g, 4.61mmol). The crude product was purified on neutral alumina in a gradient of 0-2% methanol in toluene. Pooling of fractions containing the faster running component afforded a gum which was treated with ethereal hydrogen chloride to give the **title compound** as a white solid (0.29g) m.p. 246-247°C (from methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.68-2.08 (4H, m), 2.13-2.19 (1H, m), 2.47-2.59 (1H, m), 2.92-3.00 1H, m), 3.11-3.49 (5H, m), 4.18 (2H, d, 8Hz), 7.13 (1H, dd, J=2, 7Hz), 7.38 (1H, t, J=7Hz), 7.51 (1H, t J=7Hz), 7.52 (1H, d, J=7Hz), 7.56 (1H, d, J=7Hz), 7.77 (1H, d, J=2Hz), 8.12 (1H, d, J=7Hz)

Example 8

(±)3-(5-Isoquinolinyloxy)methyl)-1-azabicyclo[2.2.2]octane hydrochloride (E8)

The title compound was prepared in a similar manner to Example 1 from (±)3-hydroxymethyl-1-azabicyclo[2.2.2]octane (0.5g, 3.55mmol), 5-hydroxyisoquinoline (0.72g, 5.32mmol), triphenylphosphine (1.21g, 4.61mmol) and diethyl azodicarboxylate (0.8g, 4.61mmol). This afforded the **title compound** as a white solid (0.19g) m.p. 277-280°C (from methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.73-2.18 (4H, m), 2.27-2.36 (1H, m), 2.71-2.86 (1H, m), 3.04-3.45 (5H, m), 3.55-3.70 (1H, m), 4.46 (2H, d, 7Hz), 7.74 (1H, d, J=7Hz), 8.02 (1H, t, J=7Hz), 8.16 (1H, d, J=7Hz), 8.56 (1H, d, J=6Hz), 8.74 (1H, d, J=6Hz), 9.92 (1H, s)

Example 9

(±) endo-3-(4-Benzylphenoxymethyl)-1-azabicyclo[2.2.1]heptane hydrochloride (E9)

The title compound was prepared in a similar manner to Example 1 from (±)endo-3-hydroxymethyl-1-azabicyclo[2.2.1]heptane (0.5g, 3.94mmol), 4-hydroxydiphenylmethane (1.09g, 5.91mmol), triphenylphosphine (1.34g, 5.12mmol) and diethyl azodicarboxylate (0.89g, 5.12mmol). This afforded the **title compound** as a white solid (0.77g) m.p. 153-156°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.83-1.93 (2H, m), 2.74-2.95 (3H, m), 3.11-3.39 (4H, m), 3.45-3.53 (1H, m), 3.90 (2H, s), 3.99-4.11 (2H, s), 6.85-6.92 (2H, m), 7.12-7.32 (7H, m).

Example 10

(±) endo-3-(4-Benzyloxyphenoxymethyl)-1-azabicyclo[2.2.1]heptane hydrochloride (E10)

The title compound was prepared in a similar manner to Example 1 from (±)endo-3-hydroxymethyl-1-azabicyclo[2.2.1]heptane (0.5g, 3.94mmol), 4-benzyloxyphenol (1.18g, 5.91mmol), triphenylphosphine (1.34g, 5.12mmol) and diethyl azodicarboxylate (0.89g, 5.12mmol). This afforded the **title compound** as a white solid (0.31g) m.p. 156-158°C (from methanol-acetone-diethyl ether).

^{1}H Nmr ($CDCl_3$) δ : 1.99-2.16 (2H, m), 2.86-2.97 (2H, m), 3.07-3.25 (3H, m), 3.28-3.36 (1H, m), 3.52-3.62 (1H, m), 3.68-3.78 (1H, m), 3.93-3.99 (1H, m), 4.03-4.08 (1H, m), 5.04 (2H, m), 6.78-6.85 (2H), 6.87-6.94 (2H, m), 7.26-7.44 (5H, m).

Example 11

(±) exo-3-(4-Benzylphenoxymethyl)-1-azabicyclo[2.2.1]heptane hydrochloride (E11)

The title compound was prepared in a similar manner to Example 1 from (±)exo- and endo-3-hydroxymethyl-1-azabicyclo[2.2.1]heptane (0.5g, 3.94mmol), 4-hydroxydiphenylmethane (1.09g, 5.91mmol), triphenylphosphine (1.34g, 5.12mmol) and diethyl azodicarboxylate (0.89g, 5.12mmol). The crude product was chromatographed on silica in a gradient of 0-20% methanol in chloroform. Pooling of pure fractions containing the major faster running component gave a gum which was converted into the hydrochloride salt to afford the **title compound** as a white solid (0.5g) m.p. 145-148°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.62-1.72 (1H, m), 1.95-2.05 (1H, m), 2.32-2.42 (1H, m), 2.78-2.83 (1H, m), 2.93-3.08 (2H, m), 3.14-3.23 (1H, m), 3.26-3.43 (3H, m), 3.84-3.94 (3H, m), 3.97-4.03 (1H, m), 6.84-6.90 (2H, m), 7.12-7.32 (7H, m).

Example 12

(±) exo-3-(4-Benzyloxyphenoxymethyl)-1-azabicyclo[2.2.1]heptane hydrochloride (E12)

The **title compound** was prepared in a similar manner to Example 1 from (±)exo- and endo-3-hydroxymethyl-1-azabicyclo[2.2.1]heptane (0.5g, 3.94mmol), 4-benzyloxyphenol (1.18g, 5.91mmol), triphenylphosphine (1.34g, 5.12mmol) and diethyl azodicarboxylate (0.89g, 5.12mmol). The crude product was chromatographed on silica in a gradient of 5-20% methanol in chloroform. Pooling of pure fractions containing the major faster running component gave a gum which was converted into the hydrochloride salt to afford the **title compound** as a white solid (0.29g) m.p. 156-158°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.72-1.87 (1H, m), 2.05-2.12 (1H, m), 2.43-2.58 (1H, m), 2.93-2.98 (1H, m), 3.06-3.50 (6H, m), 3.94-4.16 (2H, m), 5.20 (2H, m), 6.95-7.17 (4H, m), 7.42-7.65 (5H, m).

Example 13

(±) E-3-[2-(1-Naphthyl)ethenyl]-1-azabicyclo[2.2.2]octane hydrochloride (E13)

A solution of 1-azabicyclo[2.2.2]oct-3-yl carboxaldehyde (EP363085, Description 32) (1g, 7.19mmol) and diethyl 1-naphthylmethylphosphonate (2g, 7.19mmol) in tetrahydrofuran (10ml) was added over 10 min to an ice cold slurry of sodium hydride (0.216g of an 80% dispersion in mineral oil, 7.19mmol) and 15-crown-5 (60mg) in tetahydrofuran (20ml) under nitrogen (R. Baker et al., Synthesis, 1981, 117). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by the addition of acetic acid (1ml), then concentrated *in vacuo*. The residue was treated with saturated aqueous potassium carbonate (25ml) then extracted into chloroform (3 x 25ml). The combined organic extracts were dried over sodium sulphate, concentrated *in vacuo* and the residue chromatographed on neutral alumina in a gradient of 0-2% methanol in chloroform. The gum produced was converted into the HCl salt, which was washed thoroughly with diethyl ether then crystallised to afford the **title compound** as a white solid (1.4g) m.p. 196-198°C (from methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.74-2.28 (5H, m), 3.00-3.74 (7H, m), 6.58 (1H, dd, J=7, 15Hz), 7.50 (1H, d, J=15Hz), 7.55-8.12 (6H, m), 8.25-8.32 (1H, m).

Example 14

(±)E-3-[2-(4-Biphenyl)ethenyl]-1-azabicyclo[2.2.2]octane hydrochloride (E14)

The title compound was prepared in a similar manner to Example 13 from 1-azabicyclo[2.2.2]oct-3-yl-carboxaldehyde (0.78g, 5.61mmol), diethyl 4-biphenylmethyl-phosphonate (1.70g, 5.61mmol), sodium hydride (0.17g of an 80% dispersion in mineral oil, 5.61mmol) and 15-crown-5 (60mg). This afforded the **title compound** as a white solid (1.3g) m.p. 289-290°C (from methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.57-1.69 (1H, m), 1.75-1.98 (4H, m), 2.75-2.84 (1H, m), 2.94-3.29 (5H, m), 3.35-3.43 (1H, m), 6.39 (1H, dd, J=8, 16Hz), 6.52 (1H, d, J=16Hz), 7.22-7.61 (9H, m).

Example 15

(±)3-[2-(1-Naphthyl)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E15)

A mixture of (±)E-3-[2-(1-naphthyl)ethenyl]-1-azabicyclo[2.2.2[octane hydrochloride (0.7g, 2.34mmol) and 10% Pd-C (70mg) in methanol (25ml) was stirred at room temperature for 2 h under an atmosphere of hydrogen. The reaction was filtered, then concentrated *in vacuo*. The residue was treated with saturated aqueous potassium carbonate (25ml) and extracted into chloroform (3 x 25ml). The combined organic extracts were dried over sodium sulphate then concentrated *in vacuo*. The gum produced was converted into the HCl salt to afford the **title compound** as white solid (0.415g) m.p. 169-171°C (from acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.63-2.13 (8H, m), 2.76-2.85 (1H, m), 2.97-3.25 (6H, m), 3.38-3.47 (1H, m), 7.38-3.47 (1H, m), 7.38-7.59 (4H, m), 7.79 (1H, d, J=7Hz), 7.94 (1H, d, J=8Hz), 8.09 (1H, d, J=7Hz).

Example 16

(±)3-[2-(4-Biphenyl)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E16)

The title compound was prepared in a similar manner to Example 15 from (±)E-3-[2-(4-Biphenyl)ethenyl]-1-azabicyclo[2.2.2]octane hydrochloride (E14) (0.65g, 2mmol) and 10%Pd-C (65mg). This afforded the **title compound** as a white solid (0.14g) m.p. 236-238°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.52-1.91 (8H, m), 2.45-2.54 (2H, m), 2.62-2.72 (1H, m), 2.93-3.14 (4H, m), 3.22-3.32 (1H, m), 7.18-7.26 (3H, m), 7.31-7.38 (2H, m), 7.45-7.56 (4H, m).

Example 17

(±)E-3-[3-(1-Naphthyl)prop-2-enyl]-1-azabicyclo[2.2.2]octane hydrochloride (E17)

The title compound was prepared in a similar manner to Example 13 from (±)3-formylmethyl-1-azabicyclo[2.2.2]octane (0.41g, 2.68mmol), diethyl 1-naphthylmethyl-phosphonate (0.75g, 2.68mmol), sodium hydride (80mg of an 80% dispersion in mineral

oil, 2.68mmol) and 15-crown-5 (30mg). This afforded the **title compound** as a white solid (0.47g) m.p. 174-177°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.62-2.25 (6H, m), 2.35-2.54 (2H, m), 2.78-2.90 (1H, m), 3.01-3.48 (5H, m), 6.24 (1H, dt, J=7, 15Hz), 7.32 (1H, d, J=15Hz), 7.43-7.68 (4H, m), 7.78-7.96 (2H, m), 8.14-8.25 (1H, m).

Example 18

(±)3-[3-(1-Naphthyl)propyl]-1-azabicyclo[2.2.2]octane hydrochloride (E18)

The title compound was prepared in a similar manner to Example 15 from (±)E-3-[3-(1-Naphythyl)prop-2-enyl]-1-azabicyclo[2.2.2]octane hydrochloride (E17) (0.23g, 7.34mmol) and 10%Pd-C (20mg). This afforded the **title compound** as a white solid (0.16g) m.p.155°C (dec) (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.47-2.22 (10H, m), 2.73-2.92 (1H, m), 3.05-3.58 (7H, m), 7.42-7.74 (4H, m), 7.82-8.26 (3H, m).

Example 19

(±)3-[2-(2-Dibenzofuranyloxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E19)

The title compound was prepared in a similar manner to Example 1 from (±)3-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane (0.5g, 3.23mmol), 2-hydroxydibenzofuran (0.89g, 4.84mmol), triphenylphosphine (1.01g, 4.19mmol) and diethyl azodicarboxylate (0.73g, 4.19mmol). This afforded the **title compound** as a white solid (0.62g m.p 235-237°C (methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.62-2.06 (7H, m), 2.15-2.28 (1H, m), 2.80-2.94 (1H, m), 3.05-3.52 (5H, m), 4.11 (2H, t, J=6Hz), 7.09 (1h, dd, J=2,8Hz), 7.35-7.79 (5H, m), 8.12 (1H,d, J=8Hz).

Example 20

(±)3-[2-(4-Benzyloxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E20)

The title compound was prepared in a similar manner to Example 1 from (±)3-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane (0.5g, 3.23mmol), 4-benzyloxyphenol (1g, 4.84mmol), triphenylphosphine (1.01g, 4.19mmol) and diethyl azodicarboxylate (0.73g, 4.19mmol). This afforded the **title compound** as a white solid (0.5g) m.p. 215-216°C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ : 1.57-1.98 (7H, m), 2.04-2.21 (1H, m), 2.73-2.85 (1H, m), 3.00-3.40 (5H, m), 3.89 (2H, t, J=6Hz), 5.01 (2H, s), 6.79-6.96 (4H, m), 7.24-7.43 (5H, m).

Example 21

(±)3-[2-(4-Benzylphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E21)

The title compound was prepared in a similar manner to Example 1 from (±)3-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane (0.5g, 3.23mmol), 4-hydroxydiphenylmethane (0.89g, 4.84mmol), triphenylphosphine (1.01g, 4.19mmol), and diethyl azodicarboxylate (0.73g, 4.19mmol). This afforded the **title compound** as a white solid (0.69g) m.p 186-188°C (from methanol-acetone-diethyl ether).

^{1}H Nmr(DMSO-d_6) δ : 1.68-2.10 (7H, m), 2.15-2.34 (1H, m), 2.83-2.98 (1H, m), 3.10-3.58 (5H, m,), 3.95 (2H, s), 4.03 (2H, t, J=7Hz), 6.82-6.93 (2H, m), 7.17-7.42 (7H, m).

Example 22

(±)3-(4-Phenoxyphenoxymethyl)-1-azabicyclo[2.2.2]octane hydrochloride (E22)

The title compound was prepared in a similar manner to Example 1 from (±)3-hydroxymethyl-1-azabicyclo[2.2.2]octane (0.5g, 3.55mmol), 4-phenoxyphenol (0.99g, 5.32mmol), triphenylphosphine (1.21g, 4.61mmol) and diethyl azodicarboxylate (0.80g, 4.61mmol). This afforded the **title compound** as a white solid (0.59g) m.p 176-178°C (methanol-acetone-diethyl ether.

^{1}H Nmr (DMSO-d_6) δ : 1.62-2.03 (4H, m), 2.07-2.14 (1H, m), 2.40-2.55 (1H, m), 2.86-2.96 (1H, m), 3.07-3.48 (5H, m), 4.05 (2H, d, J=7Hz), 6.98-7.11 (7H, m), 7.28-7.40 (2H, m).

Example 23

(±) 3-[2-(4-Phenoxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E23)

The title compound was prepared in a similar manner to Example 1 from (±) 3-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane (0.5g, 3.22mmol), 4-phenoxyphenol (0.90g, 4.84 mmol), triphenylphosphine (1.0g, 4.19 mmol) and diethyl azodicarboxylate 0.66 ml, 4.19 mmol). After stirring at room temperature for 2h, the reaction was concentrated *in vacuo*. The residue was extracted into diethyl ether, and treated with ethereal hydrogen chloride. The resulting hydrochloride salt was washed with diethyl ether and recrystallised to give the **title compound** as a colourless solid (0.7g) m.p. 182-185^{o}C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ:1.70-2.13 (7H, m, overlapping signals), 2.28 (1H,m), 2.95 (1H, m), 3.12-3.55 (6H, m), 4.07(2H, t, J=7Hz), 6.94-7.20 (7H, m), 7.45(2H, t, J=7Hz)

Example 24

(±) 3-[4-(2-Dibenzofuranyloxy)butyl]-1-azabicyclo[2.2.2]octane hydrochloride (E24)

The title compound was prepared in a similar manner to Example 1 from (±) 3-(4-hydroxybutyl)-1-azabicyclo[2.2.2]octane (0.5g, 2.73 mmol), 2-hydroxydibenzofuran (0.75g, 4.09 mmol), triphenylphosphine (0.93g, 3.55 mmol) and diethyl azodicarboxylate (0.56 ml, 3.55 mmol). After stirring at room temperature for 1h the reaction was concentrated *in vacuo*. The crude product was converted into the hydrochloride salt, washed with diethyl ether, then partitioned betwen saturated aqueous potassium carbonate (25 ml) and chloroform (25 ml). The aqueous layer was further extracted with chloroform (2x25 ml), and the combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. Flash chromatography on alumina using 0.5-2% methanol in toluene as eluant, followed by treatment with ethereal hydrogen chloride afforded the **title compound** as a colourless solid (0.31g) m.p. 242-244^{o}C (from methanol-diethyl ether).

^1H Nmr (DMSO-d_6) δ: 1.25-2.10 (12H, m, overlapping signals), 2.69 (1H, m), 2.94-3.50 (5H, m, overlapping signals), 4.08 (2H, t, J=7Hz), 7.08 (1H, dd, J=7Hz, 2Hz), 7.28-7.78 (5H, m, overlapping signals), 8.13 (1H, d, J=7Hz).

Example 25

(±) 3-[4-(4-Phenoxyphenoxy)butyl]-1-azabicyclo[2.2.2]octane hydrochloride (E25)

The title compound was prepared in a similar manner to Example 1 from (±) 3-(4-hydroxybutyl)-1-azabicyclo [2.2.2]octane (0.5g, 2.73 mmol), 4-phenoxyphenol (0.76g, 4.09 mmol), triphenylphosphine (0.93g, 3.55 mmol) and diethyl azodicarboxylate (0.56ml, 3.55 mmol). After stirring at room temperature for 1h the reaction was worked up as described in Example 24. Purification by chromatography on neutral alumina using 0-2% methanol in chloroform as eluant, followed by treatment with ethereal hydrogen chloride afforded the **title compound** as a colourless solid (0.35g) m.p. 151-153°C (from methanol-diethyl ether).

^1H Nmr (DMSO-d_6) δ: 1.35-2.16 (12H, m, overlapping signals), 2.78 (1H, m), 3.10-3.60 (5H, m, overlapping signals), 4.03 (2H, t, J=7Hz), 6.89-7.22 (7H, m), 7.43 (2H, m).

Example 26

(±) 3-[3-(4-Phenoxyphenoxy)propyl]-1-azabicyclo[2.2.2]octane hydrochloride (E26)

The title compound was prepared in a similar manner to Example 1 from (±)3-(3-hydroxypropyl)-1-azabicyclo[2.2.2]octane (0.45g, 2.66 mmol), 4-phenoxyphenol (0.74g, 3.98 mmol), triphenylphosphine (0.91g, 3.47 mmol) and diethyl azodicarboxylate (0.55 ml, 3.47 mmol). After stirring at room temperature for 1h the reaction was worked up as described in Example 24. Purification by chromatography on neutral alumina using 0-2% methanol in chloroform as eluant, followed by treatment with ethereal hydrogen chloride afforded the **title compound** as a colourless solid (0.7g) m.p. 149-151°C (from methanol-acetone-diethyl ether).

^1H Nmr (DMSO-d_6) δ: 1.54-2.20 (10H, m, overlapping signals), 2.80 (1H, m), 3.10-3.60 (5H, m, overlapping signals), 4.05 (2H, t, J=7Hz), 6.90-7.28 (7H, m), 7.43 (2H, t, J=8Hz)

Example 27

(±) 3-[2-[4-(2-Phenylethyl)phenoxy]ethyl]-1-azabicyclo [2.2.2]octane hydrochloride (E27)

The title compound was prepared in a similar manner to Example 1 from (±) 3-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane (0.5g, 3.23 mmol), *trans* 4-hydroxystilbene (0.95g, 4.84 mmol), triphenylphosphine (1.1g, 4.19 mmol) and diethyl azodicarboxylate (0.66 ml, 4.19 mmol). After stirring at room temperature for 1.5h the reaction was concentrated *in vacuo*. The residue was extracted into diethyl ether and treated with ethereal hydrogen chloride to give the hydrochloride salt which was washed with diethyl ether. A solution of this salt in ethanol (40 ml) was hydrogenated over 10% Pd-C (0.25g) at atmospheric pressure for 4h. After removal of the catalyst by filtration through kieselguhr, the filtrate was concentrated *in vacuo*. The residue was partitioned between saturated aqueous potassium carbonate (30 ml) and chloroform (25 ml). The aqueous phase was further extracted with chloroform (2x25 ml), and the combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. Purification by chromatography on neutral alumina using 0-2% methanol in chloroform as eluant afforded an oil which was treated with ethereal hydrogen chloride to give the **title compound** as a colourless solid (0.67g) m.p. 210-212^{o}C (from methanol-acetone-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.55-2.05 (7H, m), 2.16 (1H, m), 2.82 (4H, m), 3.15 (4H, m), 3.38 (2H, m), 3.94 (2H, t, J=7Hz), 6.82 (2H, t, J=8Hz), 7.03-7.36 (7H, m).

Example 28

(±) 3-[2-[4-[2-(4-Chlorophenyl)ethyl]phenoxy]ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E28)

The title compound was prepared in a similar manner to Example 1 from (±) 3-(2-hydroxyethyl)-1-azabicyclo [2.2.2]octane (0.5g, 3.22 mmol), 4-[2-(4-chlorophenyl)ethyl]phenol (1.13g, 4.86 mmol), triphenylphosphine (1.10g, 4.20 mmol) and diethyl azodicarboxylate (0.66 ml, 4.20 mmol). The reaction was worked up as described in Example 24. Purification by chromatography on neutral alumina using 0-2% methanol in chloroform as eluant followed by treatment with ethereal hydrogen chloride afforded the **title compound** as a colourless solid (0.56 g) m.p. 220-222^{o}C (from methanol-acetone-diethyl ether).

^1H Nmr (DMSO-d_6) δ: 1.55-2.00 (7H, m), 2.16 (1H, m), 2.82 (4H, m), 3.15 (4H, m), 3.37 (2H, m), 3.95 (2H, t, J=7Hz), 6.82 (2H, d, J=7Hz), 7.10 (2H, d, J=7Hz), 7.22 (2H, d, J=7Hz), 7.30 (2H, d, J=7Hz)

Example 29

(±) 3-[2-[5-(2-Phenyl)benzo[b]furanyloxy]ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E29)

The title compound was prepared in a similar manner to Example 1 from (±) 3-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane (0.25g, 1.61 mmol), 5-hydroxy-2-phenylbenzo[b]furan (0.48g, 2.42 mmol), triphenylphosphine (0.59g, 2.25 mmol) and diethyl azodicarboxylate (0.36ml, 2.25 mmol). The reaction was worked up as described in Example 24. Purification by chromatography on neutral alumina using 0-2% methanol in chloroform as eluant followed by treatment with ethereal hydrogen chloride afforded the **title compound** as a colourless solid (0.35g), m.p. 266-267°C (from methanol-acetone-diethyl ether).

^1H Nmr (DMSO-d_6) δ: 1.70-2.15 (7H, m), 2.30 (1H, m), 2.95 (1H, m), 3.14-3.62 (5H, m), 4.13 (2H, t, J=7Hz), 7.00 (1H, dd, J=7Hz, 2Hz), 7.27 (1H, d, J=2Hz), 7.40-7.68 (5H, m), 8.00 (2H, d, J=7Hz).

Example 30

(±) 2-[2-(4-Benzylphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E30)

The title compound was prepared in a similar manner to Example 1 from (±) 2-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane (23mg, 0.15 mmol), 4-hydroxydiphenylmethane (41mg, 0.22 mmol), triphenylphosphine (59 mg, 0.22 mmol) and diethyl azodicarboxylate (39 mg, 0.22 mmol). After stirring at room temperature for 6h the reaction mixture was concentrated *in vacuo*. The residue was partitioned between water (5 ml) and chloroform (5ml) and the pH of the aqueous phase was adjusted to 12 with potassium carbonate. After further extraction with chloroform (3x5ml) the combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. Chromatography on neutral alumina using 0-5% ethanol in chloroform as eluant, followed by treatment with ethereal hydrogen chloride afforded the hydrochloride salt which was washed with diethyl ether and recrystallised to give the **title compound** as a colourless solid (34 mg) m.p. 177-178.5°C (from acetone-diethyl ether).

^1H Nmr (DMSO-d_6) δ: 1.50 (1H, m), 1.73 (4H, m), 1.95-2.13 (3H, m), 2.32 (1H, m), 3.07-3.40 (4H, m), 3.57 (1H, m), 3.87 (2H, s), 4.05 (1H, m), 6.86 (2H, d, J=7Hz), 7.10-7.30 (7H, m).

Example 31

(±) 2-[2-(4-Benzyloxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E31)

The title compound was prepared in a similar manner to Example 30 from (±) 2-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane (0.5g, 3.22mmol), 4-benzyloxyphenol (0.97g, 4.84mmol), triphenylphosphine (1.27g, 4.84mmol) and diethyl azodicarboxylate (0.76ml, 4.84mmol). This afforded the title compound as a colourless solid (0.69g) m.p. 238-240°C (from acetone-diethyl ether).

^1H Nmr (DMSO-d_6) δ: 1.70 (1H, m), 1.96 (4H, m), 2.19 (3H, m), 2.50 (1H, m), 3.28 (1H, m), 3.45 (3H, m), 3.74 (1H, m), 4.19 (2H, m), 5.22 (2H, s), 7.10 (4H, q, J=9Hz), 7.58 (5H, m), 10.47 (1H, br.s).

Example 32

(±) 2-[2-(4-Phenoxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane hydrochloride (E32)

The title compound was prepared in a similar manner to Example 30 from (±) 2-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane (0.5g, 3.22mmol), 4-phenoxyphenol (0.90g, 4.84mmol), triphenylphosphine (1.27g, 4.84mmol) and diethyl azodicarboxylate (0.76ml, 4.84mmol). This afforded the title compound as a colourless solid (0.74g) m.p. 200-202°C (from acetone-diethyl ether)

^1H Nmr ($CDCl_3$) δ: 1.70 (2H, m), 1.93 (4H, m), 2.08 (1H, m), 2.26 (2H, m), 2.82 (1H, m), 3.37 (4H, m), 3.53 (1H, m), 4.18 (2H, m), 6.95 (7H, m), 7.30 (2H, m), 12.02 (1H, br.s).

Example 33

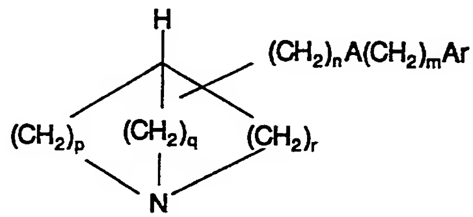
(±) 4-[2-(4-Phenoxyphenoxy)ethyl]-1-azabicyclo[3.3.1]nonane hydrochloride (E33)

The title compound was prepared in a similar manner to Example 1 from (±) 4-(2-hydroxyethyl)-1-azabicyclo[3.3.1]nonane (0.11g, 0.65 mmol), 4-phenoxyphenol (0.18g, 0.98 mmol), triphenylphosphine (0.22g, 0.85 mmol) and diethyl azodicarboxylate (0.13 ml, 0.85 mmol). After stirring at room temperature for 2h the reaction was worked up as described in Example 1 to give the **title compound** as a colourless solid m.p. 195-197^{o}C (methanol-diethyl ether).

^{1}H Nmr (DMSO-d_6) δ: 1.53-2.30 (10H, m), 3.05-3.60 (6H, m), 4.00 (2H, t, J=7Hz), 6.83-7.20 (7H, m), 7.35 (2H, t, J=7Hz).

Claims :

1. Use of a compound of formula (I):



Formula (I)

in which

p, q and r each independently represent an integer from 1 to 4;

A is a bond, -CH=CH-, -C≡C-, oxygen, sulphur or NR^1, where R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl;

n is 0 to 6, and m is 0 to 6, such that the length of the chain $(CH_2)_nA(CH_2)_m$ is at least two atoms; and

Ar is aryl or heteroaryl, each of which may be optionally substituted;

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of disorders where a calcium channel antagonist is indicated.

2. Use of a compound according to claim 1 wherein the disorder is a condition or disease related to an accumulation of calcium in the brain cells of a mammal.

3. Use according to claim 1 or claim 2 wherein the disorder is anoxia, ischaemia, migraine, epilepsy, traumatic head injury, drug addiction withdrawal or AIDS-related dementia.

4. Use of a compound according to any of claims 1 to 3 wherein p and r are independently 2 or 3.

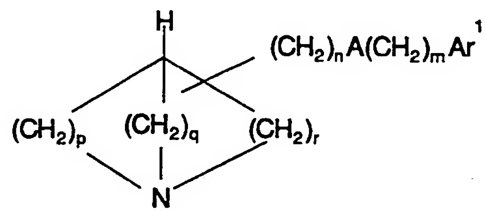
5. Use of a compound according to any of claims 1 to 4 wherein q is 1 or 2.

6. Use of a compound according to any of claims 1 to 5 wherein A is oxygen, -CH=CH- or a bond.

7. Use of a compound according to any of claims 1 to 6 wherein the length of the chain $-(CH_2)_nA(CH_2)_m$ is from 2 to 6 atoms.

8. Use of a compound according to any of claims 1 to 7 wherein m is 0 to 3.

9. A compound of formula (IA) :



Formula (IA)

in which

p, q and r each independently represent an integer from 1 to 4;
n is 0 to 6;
m is 0 to 6; and
either

A is -C≡C- or NR^1, where R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl; in which case Ar^1 represents the group Ar as hereinbefore defined;

or A is a bond, in which case Ar^1 represents the group Ar as hereinbefore defined with the proviso that when each of p, q and r is 2 and Ar is phenyl substituted by one or two groups selected from halogen, C_{1-4}alkoxy, nitro, cyano or amino, then the group $-(CH_2)_nA(CH_2)_m$ is not C_{1-4}alkyl α to the quinuclidine nitrogen atom or C_{2-4}alkyl β to the quinuclidine nitrogen atom,

or A is -CH=CH- in which case Ar^1 represents the group Ar as hereinbefore defined with the proviso that when each of p, q and r is 2; n and m are both zero and Ar is mono- or di-chlorophenyl, the group $-(CH_2)_nA(CH_2)_m$ is not β to the quinuclidine nitrogen atom.

or A is oxygen or sulphur in which case Ar^1 represents a group Ar^2 which is phenyl substituted by a C_{1-2}alkylenedioxy group or by 1 to 3 substituents selected from SC_{1-4}alkyl, OCF_3, CF_3, optionally substituted phenoxy, optionally substituted phenylC_{1-4}alkyl and optionally substituted phenylC_{1-4}alkoxy; or Ar^2 is

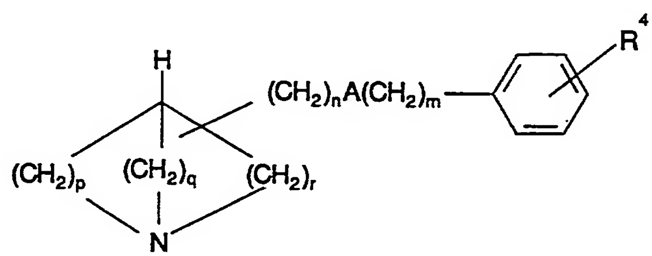
an optionally substituted bicyclic or tricyclic aryl group of up to 15 carbon atoms;

an optionally substitued benzofuranyl group; or

an optionally substituted tricyclic heteroaryl group;

or a salt thereof.

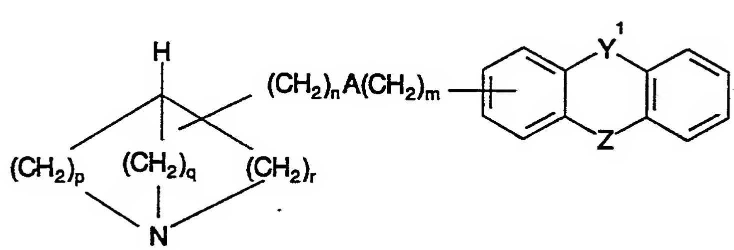
10. A compound of formula (IB) :



Formula (IB)

wherein p, q, r, n, m and A are as defined for formula (IA) and R^4 represents optionally substituted phenoxy, optionally substituted phenylC_{1-4}alkyl or optionally substituted phenylC_{1-4}alkoxy, or R^4 represents a fused benzene ring; or a salt thereof.

11. A compound of formual (IC) :



Formula (IC)

wherein p, q, r, n, m and A are as defined for formula (IA) and Y^1 and Z are as hereinbefore defined for formula (I); or a salt thereof.

12. A compound according to any of claims 9 to 11 wherein m is 0 to 3.

13. A compound of formula (I) selected from :

(±)3-(3,4-dichlorophenoxymethyl)-1-azabicyclo[2.2.2]octane;
(±)3-(4-benzyloxyphenoxymethyl)-1-azabicyclo[2.2.2]octane;
(±)3-(4-benzylphenoxymethyl)-1-azabicyclo[2.2.2]octane;
(±)3-(2-phenylphenoxymethyl)-1-azabicyclo[2.2.2]octane;
(±)3-(4-tert-butylphenoxymethyl)-1-azabicyclo[2.2.2]octane;
(±)3-(1-naphthyloxymethyl)-1-azabicyclo[2.2.2]octane;
(±)3-(2-dibenzofuranyloxymethyl)-1-azabicyclo[2.2.2]octane;
(±)3-(5-isoquinolinyloxy)methyl)-1-azabicyclo[2.2.2]octane;
(±) endo-3-(4-benzylphenoxymethyl)-1-azabicyclo[2.2.1]heptane;
(±) endo-3-(4-benzyloxyphenoxymethyl)-1-azabicyclo[2.2.1]heptane;
(±) exo-3-(4-benzylphenoxymethyl)-1-azabicyclo[2.2.1]heptane;
(±) exo-3-(4-benzyloxyphenoxymethyl)-1-azabicyclo[2.2.1]heptane;
(±) E-3-[2-(1-naphthyl)ethenyl]-1-azabicyclo[2.2.2]octane;
(±)E-3-[2-(4-biphenyl)ethenyl]-1-azabicyclo[2.2.2]octane;
(±)3-[2-(1-naphthyl)ethyl]-1-azabicyclo[2.2.2]octane;
(±)3-[2-(4-biphenyl)ethyl]-1-azabicyclo[2.2.2]octane;
(±)E-3-[3-(1-naphthyl)prop-2-enyl]-1-azabicyclo[2.2.2]octane;
(±)3-[3-(1-naphthyl)propyl]-1-azabicyclo[2.2.2]octane;
(±)3-[2-(2-dibenzofuranyloxy)ethyl]-1-azabicyclo[2.2.2]octane;
(±)3-[2-(4-benzyloxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane;
(±)3-[2-(4-benzylphenoxy)ethyl]-1-azabicyclo[2.2.2]octane;
(±)3-(4-phenoxyphenoxymethyl)-1-azabicyclo[2.2.2]octane;

(±) 3-[2-(4-phenoxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane,

(±) 3-[4-(2-dibenzofuranyloxy)butyl]-1-azabicyclo[2.2.2]octane,

(±) 3-[4-(4-phenoxyphenoxy)butyl]-1-azabicyclo[2.2.2]octane,

(±) 3-[3-(4-phenoxyphenoxy)propyl]-1-azabicyclo[2.2.2]octane,

(±) 3-[2-[4-(2-phenylethyl)phenoxy]ethyl]-1-azabicyclo [2.2.2]octane,

(±) 3-[2-[4-[2-(4-chlorophenyl)ethyl]phenoxy]ethyl]-1-azabicyclo[2.2.2]octane,

(±) 3-[2-[5-(2-phenyl)benzo[b]furanyloxy]ethyl]-1-azabicyclo[2.2.2]octane,

(±) 2-[2-(4-benzylphenoxy)ethyl]-1-azabicyclo[2.2.2]octane,

(±) 2-[2-(4-benzyloxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane,

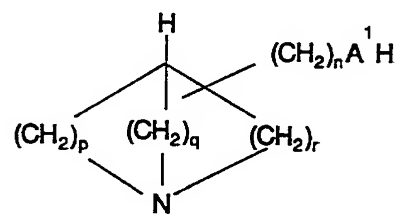
(±) 2-[2-(4-phenoxyphenoxy)ethyl]-1-azabicyclo[2.2.2]octane, and

(±) 4-[2-(4-phenoxyphenoxy)ethyl]-1-azabicyclo[3.3.1]nonane,

or a salt thereof.

14. A process for the preparation of a novel compound of formula (I) which comprises:

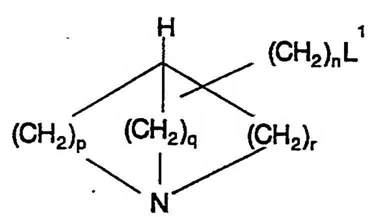
(a) for compounds of formula (I) in which A is O, S or NR^1, reaction of a compound of formula (II):



Formula (II)

in which p, q, r and n are as described for formula (I) and A^1 is O, S or NR^1, with a compound of formula $L(CH_2)_mAr$ in which m and Ar are as described for formula (I), and L is a leaving group;

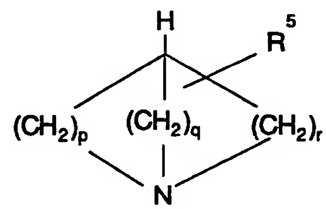
(b) for compounds of formula (I) in which A is O, S or NR^1, reaction of a compound of formula (III):



Formula (III)

in which p, q, r and n are as described for formula (I) and L^1 is a group displaceable by a nucleophile, with a compound of formula $HA^1(CH_2)_mAr$ where m and Ar are as described for formula (I) and A^1 is as described for formula (II); or

(c) for compounds of formula (I) in which A is NR^1, reduction of a compound of formula (IV) :



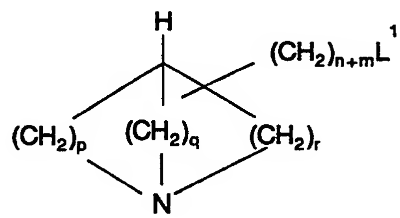
Formula (IV)

in which R^5 represents the group

$-(CH_2)_nN(R^1)C(O)(CH_2)_{m-1}Ar$ or $-(CH_2)_{n-1}C(O)N(R^1)(CH_2)_mAr$,

and p, q, r, n, m, and Ar are as described for formula (I);

(d) for compounds of formula (I) in which A is a bond, reaction of a compound of formula (V) :

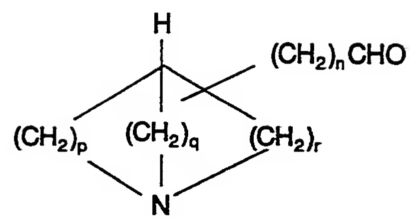


Formula (V)

(wherein L^1, p, q, r, m and n are as hereinbefore defined).

with a compound of formula X^1Ar in which Ar is as described for formula (I), and X^1 is an alkali metal;

(e) For compounds wherein A is -CH=CH- reaction of a compound of formula (VI) :



Formula (VI)

(wherein n, p, q and r are as hereinbefore defined) with a Wittig reagent serving to introduce the group Ar;

(f) Interconversion of one compound of formula (I) to a different compound of formula (I) e.g. the reduction of a compound wherein A is -CH=CH- to a compound wherein A is $-CH_2CH_2-$;

and optionally thereafter forming a salt.

15. A pharmaceutical composition comprising a novel compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

16. A method of treatment of a condition or disease related to the accumulation of calcium in the brain cells of a mammal which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00175

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D453/02; A61K31/395; C07D487/08; C07D471/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0 412 797 (MERCK SHARP & DOHME LTD.) 13 February 1991 * example 10, 19-21,25,37,43,47 * ---	9
X	EP,A,0 327 155 (MERCK SHARP & DOHME LTD.) 9 August 1989 * example2, 4-6,8, etc. * ---	9
X	WO,A,9 114 686 (NOVO NORDISK A/S) 3 October 1991 * complete document * ---	9
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° Special categories of cited documents : [10]

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IV. CERTIFICATION

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Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08 APRIL 1993	13. 05. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VAN BIJLEN H.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

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The members are as contained in the European Patent Office EDP file on 08/04/93
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82